## REMARKS

In response to the Office Action dated May 5, 2006, Applicants submit the following remarks. The three-month extended deadline for filing a response falls on August 5, 2006. A one-month Petition for Extension of Time and the required fee are filed herewith. Therefore, Applicants believe that this response is being timely filed. In the event that there are any additional fees required in connection with this response, please charge any necessary fee to Deposit Account No. 23-2415, referencing Docket No. 30797-717.201.

Claim 1 has been amended to include the elements formerly claimed in dependent claim 3 and does not add new matter. Claims 1, 4, 5 and 7-11 have been amended to include "human" TGFα. Support for such an amendment can be found throughout the specification and claims as filed and does not add new matter. Withdrawn claims 14-18 have been amended to place the claims in the standard "method" format of claims in U.S. applications. The amendments to the claims do no more than facilitate the translation from Spanish to English and do not add any new matter. New claim 19 depends from claim 18 and removes the exemplary "other ligand" from claim 18 to create the correct dependency format according to U.S. practice.

In view of the remarks and amendments submitted herein, Applicants believe that the Application is in condition for allowance and such favorable action is earnestly solicited.

Applicants submit that the claims as currently recited are allowable and request rejoinder of withdrawn method claims 14-18 and new claim 19 which have been amended to be consistent with the composition claims in accordance with *In re Ochiai* 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995); and *In re Broewer* 77 F.3d 422, 37 USPQ2d 1663 (Fed. Cir. 1996).

By the above amendments, Applicants have amended the claims to expedite prosecution of the subject application. However, Applicants reserve the right to resubmit the cancelled subject matter in one or more continuation applications without prejudice.

Applicants acknowledge withdrawal of the following objections and rejections:

1. The objection to the specification;
2. The objection to the dependent claims;
3. The rejection of claims 1-13 under 35 U.S.C. § 112, second paragraph;
4. The rejection of claims 1-9, 12 and 13 under 35 U.S.C. §§ 112, first paragraph – enablement and written description;
5. The rejection of claims 1, 3, and 13 under 35 U.S.C. § 102(b) as being anticipated by Gonzalez (Gonzalez et al., Annals of Oncology); and
6. The rejection of claims 1, 3, 12 and 13 under 35 U.S.C. § 102(b) as being anticipated by Gonzalez (Gonzalez et al., Vaccine Research).

**The Examiner has maintained the following claim rejections:**

1. Claims 1 and 2 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by either Heimbrook (Heimbrook, D.C. et al. PNAS, 87: 4697-4701, 1990) or Kunwar (Kunwar, S. et al. J. Neurosurg., 79: 569-576, 1993) as evidenced by Chaundhary (Chaundhary, V.K. et al. PNAS, USA, 84: 4538-4542, 1987).

The Examiner maintained the rejection for the reasons of record. Specifically, the Examiner states at pages 4-5 of the Office Action that:

> Claims 1 and 2 are interpreted broadly to include compositions comprising a fusion protein or conjugate of TGFα and a carrier protein with an intended use as a vaccine.
>
> Heimbrook teaches a fusion protein of human TGFα and PE40 (40kDa segment of the Pseudomonas exotoxin A protein) in combination with phosphate buffered saline (interpreted to be within the scope of an "adjuvant") (see 4698, 1st – 2nd column and 4699, 1st – 2nd column).
>
> Kunwar also teaches a fusion protein of human TGFα and PE40 (see Chaudhary for evidence that Kunwer's [*sic*] TGFα is human TGFα, page 4538, 2nd column). Kunwer [*sic*] teaches the fusion protein in combination with human serum albumin (interpreted to be within the scope of an "adjuvant", see page 570, 2nd column, "Recombinant Proteins").

> Kunwer [*sic*] also teaches that the fusion protein construct is immunogenic (see page 574, 2nd column). Therefore, either Heimbrook or Kunwar teaches a composition that is the same as that claimed.
>
> Applicants did not specifically argue the merits of this rejection except to state that none of the cited references teach TGFα that comprises the amino acid sequence of SEQ ID NO: 2. This argument is not found persuasive because the amino acid sequence of SEQ ID NO: 2 appears to be the sequence of human TGFα, and both of the above cited references teach human TGFα. Therefore, the rejection is maintained.

Presently claim 1 recites "[a] A vaccine composition containing human TGFα "hTGFα", wherein said hTGFα comprises the amino acid sequence of SEQ ID NO 2 or its combination with other EGF-R ligands, coupled with any carrier protein by genetic cloning before expression of said proteins or by chemical conjugation after expression of said proteins, wherein said vaccine contains an adjuvant, wherein said vaccine is able to produce a specific immune response against said hTGFα, and wherein said carrier protein is P64k."

a. None of the cited references teach or suggest a vaccine composition as currently claimed wherein said carrier protein is P64k.

b. The Examiner stated that Applicants' arguments of record are not found persuasive because the amino acid sequence of SEQ ID NO: 2 appears to be the sequence of human TGFα, and both of the above cited references (i.e., Heimbrook and Kunwar) teach human TGFα.

Applicants respectfully disagree. The Examiner has taken Official Notice that the human TGFα described by Heimbrook and Kunwar is SEQ ID NO: 2; however, the Examiner has provided no *objective* evidence that the protein described by Heimbrook and Kunwar is the protein having the amino acid sequence of SEQ ID NO: 2 *per se*. A mere statement that the amino acid sequence of SEQ ID NO: 2 *appears* to be the sequence of human TGFα is not sufficient grounds for rejecting the claims under 35 U.S.C. § 102(b) which requires that each and every element be disclosed in the cited reference. MPEP § 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Neither

Heimbrook nor Kunwar provide the amino acid sequence of the protein used in their experiments that is described as TGFα or provide a GenBank reference number for the protein.

Heimbrook teaches at column 1 of page 4697, that the TGFα domain is *derived from* a synthetic gene encoding the mature form of human TGFα as referenced by Defoe-Jones et al., *Mol. Cell. Biol.* 8: 2999-3007 (1988) (*see* Exhibit A). Heimbrook does not teach or suggest the actual sequence that was derived from the synthetic gene of Defoe-Jones et al. Therefore, one skilled in the art could not determine what the reference sequence actually is, or if sequence modifications were made as part of the derivation process. Applicants respectfully submit that the Examiner has failed to show that the TGFα described by Heimbrook is the protein having the amino acid sequence of SEQ ID NO: 2 as required by claim 1. As claim 2 depends from claim 1, the argument also holds true for the dependent claim.

Kunwar teaches a fusion protein of human TGFα and PE40 in the *Recombinant Proteins* section of the Materials and Methods. Kunwar does not teach or suggest the amino acid sequence of the TGFα protein; therefore, it does not teach or suggest a protein having an amino acid sequence of SEQ ID NO: 2. One skilled in the art could not determine what the reference sequence actually is. The Examiner points to Chaudhary for evidence that Kunwar's TGFα is human TGFα (page 4538, 2nd column). The claim as currently recited requires that the TGFα protein have the amino acid sequence of SEQ ID NO: 2. Merely stating that the protein is TGFα does *not* provide conclusive evidence that the TGFα has the amino acid sequence of SEQ ID NO: 2.

Chaudhary fails to teach or suggest a protein having the amino acid sequence of SEQ ID NO: 2. Chaudhary teaches in the Materials and Methods section of the reference that a plasmid, phTGFα10-295 was a gift from Graeme I. Bell. Chaudhary does not teach or suggest the actual sequence of the TGFα that was present in the plasmid and does not provide objective evidence that the TGFα is the same as the protein having the amino acid sequence of SEQ ID NO: 2 *per se* as required by claim 1. Therefore, Chaudhary does not provide evidentiary evidence that the protein described in the reference is a protein having the amino acid sequence of SEQ ID NO: 2

*per se* as required by claim 1 and cannot serve as an evidentiary reference to support the Heimbrook or Kunwar reference.

The Courts have made clear that a reference is only good for what it clearly and definitely discloses. *In re Hughes*, 496 F.2d 1216 (CCPA 1974). In this case, Heimbrook and Kunwar fail to teach or suggest a TGFα protein having the amino acid sequence of SEQ ID NO: 2 as required by the claims. Chaudhary fails to provide the amino acid sequence of SEQ ID NO: 2 and, thus, fails to act as an evidentiary reference. Thus, the references, either alone or in combination, fail to disclose the combination of elements required by the claims.

Applicants respectfully traverse the Examiner's Official Notice in this case and request that the Examiner provide objective evidence in the form of a literature reference or provide an Examiner's affidavit to support the assertions of record, or withdraw the rejection as the references fail to disclose each and every element of the recited claims as required to make a rejection under 35 U.S.C. § 102(b).

As such, Applicants submit that for this reason alone, Heimbrook or Kunwar, both as evidenced by Chaudhary fail to disclose the combination of elements as recited in claims 1 and 2.

Supplemental reasons for traversal of the rejection are also provided herewith as follows:

c. The Heimbrook reference

The Examiner stated that the Heimbrook reference has been read broadly such that phosphate buffered saline has been interpreted as an adjuvant and pointed to pages 4698 and 4699 as supporting this assertion.

Applicants respectfully traverse this statement and submit that the Examiner has mis-characterized the teachings of Heimbrook.

As defined by biology dictionaries, an adjuvant is "a substance that, when added to a medicine, speeds or improves its action which aids another, such as an auxiliary remedy," or "a substance added to a vaccine to improve the immune response so that less vaccine is needed to

produce a non-specific stimulator (for example, BCG vaccine) of the immune response." See adjuvant definition from Biology-Online.org (Exhibit B).

It is well known in the art that phosphate buffered saline (PBS) is a widely used carrier in many applications, including *in vitro* and *in vivo* procedures, precisely because it functions as a carrier that does *not* change the properties of the material being administered or applied in culture. PBS is a buffer solution used to stabilize the pH of an aqueous solution.

Heimbrook does not teach anywhere on page 4698 or 4699 that PBS could, even remotely, be considered an adjuvant in contrast to the Examiner's assertions.

Applicants arguments are supported by the content of the Heimbrook reference at Figure 2 and the 2nd column of page 4699. Specifically, the description of Figure 2 at the bottom of page 4699 illustrates that PBS was used as the control in the experiment as the distinction was made in the experiment between injection of PBS alone and the fusion protein in PBS. One skilled in the art would recognize PBS was used as the control in this experiments *because* it would not be expected to exert any effects on the mice and, thus, any results observed would be due solely to the action of the fusion protein. This reasoning can also be observed in the description of Figure 3 at the bottom of page 4700. Applicants submit that the Examiner has extended the disclosure of the Heimbrook reference beyond teachings of the reference as well as beyond that which is well known in the art.

In conclusion, Applicants assert that the Heimbrook reference cannot be ready broadly to the point that PBS would be considered an adjuvant as set forth by the Examiner, and the Heimbrook reference cannot serve as an anticipatory reference alone or in combination with Chaudhary because the reference fails to disclose an adjuvant as required by claims 1 and 2.

d. The Kunwar reference

The Examiner has stated that the Kunwar reference has been read broadly such that human serum albumin has been interpreted as an adjuvant and pointed to page 570, 2nd column, "Recombinant Proteins" as supporting this assertion.

Applicants respectfully submit that the Examiner has mischaracterized the teachings of the reference and, indeed, made an assertion that is contrary to the common and well known use of human serum albumin to stabilize proteins in solution. Furthermore, human serum albumin is not an immunogen when administered to humans.

As defined by biology dictionaries, an adjuvant is "a substance that, when added to a medicine, speeds or improves its action which aids another, such as an auxiliary remedy," or "a substance added to a vaccine to improve the immune response so that less vaccine is needed to produce a non-specific stimulator (for example, BCG vaccine) of the immune response." See adjuvant definition from Biology-Online.org (Exhibit B) discussed *supra*.

It is well known in the art that human serum albumin stabilizes proteins in solution and acts to extend the serum half-life of the material being administered or applied in culture.

At no point does Kunwar teach or suggest that human serum albumin could be used as an adjuvant.

Applicants' arguments are supported by the content of the Kunwar reference in the "Stability of TP40" section of the Materials and Methods on page 570. Specifically, Kunwar teaches that the TP40 was in solution containing 0.2% human serum albumin. Thus, the human serum albumin was clearly added to stabilize to protein in solution, *not* to act as an adjuvant. Applicants' arguments are further supported by the teaching at the section entitled "Stability of TP40" in the 2nd column of page 572, in which Kunwar teaches that in order for an agent to be administered in a miniosmotic pump, the agent must be stable. "To determine if TP40 was stable at 37°C, TP40 was diluted in PBS/0.2% human serum albumin and maintained at 37°C for 7 days." One skilled in the art would recognize human serum albumin was added to the TP40 solution in this reference is *because* it was used to stabilize the protein in solution, not to act as an adjuvant. Applicants submit that the Examiner has extended the disclosure of the Kunwar reference beyond the teachings of the reference as well as beyond that which is well known in the art.

In conclusion, Applicants assert that the Kunwar reference cannot be ready broadly to the point that human serum albumin would be considered an adjuvant as set forth by the Examiner, and the Kunwar reference cannot serve as an anticipatory reference alone or in combination with Chaudhary because the reference fails to disclose an adjuvant as required by claims 1 and 2.

Neither Heimbrook nor Kunwar teach a composition that is the same as that claimed alone or as evidenced by Chaudhary. Thus, withdrawal of the rejection under 35 U.S.C. §102(b) is believed to be in order. Such action is respectfully requested.

2. Claims 1-13 remain provisionally rejected under the judicially created doctrine of obviousness- type double patenting as allegedly being unpatentable over Claims 7, 10, 11, 12, 23 and 26 of Application No. 10/005,341.

As stated of record, Applicants respectfully request that this rejection be stayed in abeyance until the Office indicates that the present Application is otherwise in condition for allowance. At such time, Applicants will file a Terminal Disclaimer, if appropriate.

**New grounds of objection and rejection**

3. Claims 1, 2, 4, 5 and 7-11 are objected to because of the use of the term TGFα instead of human TGFα or hTGFα.

Applicants request clarification as to why claim 2 was included in this objection as it already states that the TGFα is human TGFα.

Nonetheless, Applicants submit that the objection is moot in view of the amendments to claims 1, 4, 5 and 7-11 presented herein, in the format suggested by the Examiner, and respectfully request withdrawal of the objection.

4. The specification is objected to for allegedly not being in compliance with the sequence rules. "Figure 1 contains sequences that are not identified by sequence identifier either in the figure itself or in the description of the drawings."

Applicants respectfully disagree. On November 6, 2002, a paper was entered by the USPTO which amended the specification, including the description of Figure 1, to correctly reference the sequence identifiers. A copy of the amendment as entered by the USPTO is provided herewith as Exhibit C.

As such, Applicants submit that the specification is in compliance with 37 C.F.R. §§ 1.821 through 1.825, and respectfully request withdrawal of the objection.

5. Claims 10 and 11 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement for the full scope of the claims.

The Examiner states at page 6 of the Office Action that "while being enabling for vaccines comprising an EGF molecule sufficiently characterized by physical or chemical structure, such as by SEQ ID NO, does not reasonably provide enablement for vaccines comprising EGF molecules identified solely as EGF." Further, "because of the scope of the terms 'EGF', [*sic*] as defined in the specification, in comparison with the narrow scope of the working examples provided, it appears that the specification fails to enable the full scope of the claimed vaccines.

Applicants respectively disagree. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. MPEP § 2164.03; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. MPEP § 2164.02.

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. MPEP § 2164.01; *In re Bucher*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In the present case, much has been known about the structure and function of EGF since the 1970s. The nucleic acid and amino acid sequences of EGF were disclosed as early as the 1970s. See, for example, Marquardt et al. (1983) *PNAS, USA*, 80: 4684-4688 (Exhibit D); Gray et al. *Nature*, 1983; 303: 5919) (Exhibit E):722-5; Gregory, H. (1975) *Nature* (*London*) 257: 325-327 (Exhibit F); and Savage et al. (1972) *J. Biol. Chem.* 247: 7612-7621 (Exhibit G). As early as 1984, biologically active synthetic fragments of epidermal growth factor were made and tested in assays and the major receptor-binding region was localized (Komoriya et al. PNAS, USA, 81: 1351-1355 (1984); Exhibit H).

Campbell et al. (*Prog. Growth Factor Res.* 1(1): 13-22 (1989); Exhibit I) disclosed the structures of human epidermal growth factor (EGF) and human transforming growth factor alpha (TGFα) as determined in solution using nuclear magnetic resonance (NMR) techniques. The structures produced models which could be tested in a site-directed mutagenesis program to observe sequence-activity relationships. In 1990, Campbell (Campbell et al (*Biochem Pharmacol.* 40(1): 35-40 (1990); Exhibit J) further described the structure by NMR. Campbell teaches that, as of 1990, many sequences of EGF from different species, such as, human, rat, mouse and guinea pig were known. Also, the modules or domains of extracellular proteins which have sequences homologous to EGF were known (*see* left column of page 35). Campbell discloses in the introduction that a large number of EGF variants had been produced and tested by that time and the paper resolved the structure about the variant proteins produced. Further, assays for testing the result of the function are disclosed (see right column of page 38). Therefore, as early as 1990, the structure, conserved residues among family members and

residues that are changed conservatively among family members were known and understood in the art. Additionally, sequences which were responsible for binding of EGF and TGFα to the EGF receptor were known (*see* description of Figure 1). Lastly, Campbell discusses the effect of mutations on structure and receptor binding at pages 38 and 39.

Currently, there are 5350 nucleotide submissions and 5193 amino acid submission for EGF in GenBank (see Exhibit K).

Thus, the level of skill and knowledge in the art of growth factors such as EGF is high and, therefore, the amount of information required by Applicants to show how to make and use the genus of claimed EGF molecules is low. In view of the extensive knowledge in the field of EGF and the long-known methods of making and using variant EGF molecules that retain receptor-binding ability, Applicants need not re-demonstrate in the specification what is well-established in the art. MPEP § 2164.01; *In re Bucher*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Further, Applicants do not bear the burden to disclose every operable species. Indeed, it is well established that even a single embodiment can provide broad enablement in cases involving predictable factors. *In re Vickers*, 141 F.2d 522, 526-527, 61 USPQ 122, 127 (CCPA 1974); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). In the present case, the level of knowledge of EGF was high at the time of filing. Applicants submit that the working examples, in light of the applicability of the disclosure to the genus of EGF species known in the art, are sufficient to enable one skilled in the art to practice the invention as claimed without undue experimentation.

The Examiner stated that "[b]ecause of the definition of the terms provided by the specification, the genus of molecules encompassed by the claimed vaccines is large. Furthermore, the study of the relationship between the primary amino acid sequence and protein function is highly unpredictable." The Examiner cited the following references in support of this

statement. Bowie et al. (Science, 247: 13036-1310, 1990), Burgess et al. (J. Cell Biology, 111: 2129-2138 (1990)

Applicants respectively disagree. Of note, the three references were published in 1988 and 1990. The state of the art of protein mutagenesis and analysis of protein function as a result of mutagenesis was well-developed for EGF in 1990 as discussed above with respect to Campbell. Further, the state of the art of protein mutagenesis and analysis of protein function as a result of mutagenesis for other proteins in general has developed considerably since 1990. In one non-limiting example, Wrobel (Wrobel et al., PNAS, USA, 95: 638-645 (1998); Exhibit L)) teach that a genetic approach was available for identifying amino acid residues in proteins, such as HIV-1 reverse transcriptase, which could be mutated using oligonucleotide-directed mutagenesis, to evaluate and determine the effect of the single mutation on the function of the protein using biological assays. Wrobel was published three years prior to the filing date of the present application and could have been considered by any laboratory contemplating making and testing variant proteins or peptides. Additionally, computer programs were available prior to the time of filing the present application which predict the effect of mutations, and the function of the variant proteins could be compared to the wild-type protein using biological assays as described.

Applicants submit that any experimentation to practice full scope of the claimed invention would be routine and, thus, the application is fully enabled over the full scope of the currently recited claims. Thus, withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is believed to be in order. Such action is respectfully requested.

6. Claims 10 and 11 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking written description for the full scope of the claims.

The Examiner states at page 9 of the Office Action that "[t]he basis for this rejection is that the specification fails to provide an adequate description of 'EGF'. [*sic*] This rejection is based on the interpretation of the terms "EGF" encompassing a genus of molecules that are not adequately described by the specification." Furthermore, the Examiner states at page 10 of the

office action that "the specification has failed to provide a nexus between structure and function, with which one of skill in the art may define each genus."

Written description must be determined on a case-by-case basis depending on the application at hand. Recently, the Federal Circuit has more clearly established the disclosure requirements of a specification when a broad genus of structures, in the form of nucleotide and amino acid sequences, are well-known in the art. *Capon v. Eshhar*, 418 F.3d 1349, 1360 (Fed. Cir. 2005)

Based on the facts of the case, the Federal Circuit overturned the Board's decision based on the following:

> For the chimeric genes of the Capon and Eshhar inventions, the law must take cognizance of the scientific facts. The Board erred in refusing to consider the state of the scientific knowledge, as explained by both parties, and in declining to consider the separate scope of each of the claims. None of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., Regents v. Lilly, Fiers v. Revel, Amgen, or Enzo Biochem, require a re-description of what was already known. In Lilly, 119 F.3d at 1567, the cDNA for human insulin had never been characterized. Similarly in Fiers, 984 F.2d at 1171, much of the DNA sought to be claimed was of unknown structure, whereby this court viewed the breadth of the claims as embracing a "wish" or research "plan." In Amgen, 927 F.2d at 1206, the court explained that a novel gene was not adequately characterized by its biological function alone because such a description would represent a mere "wish to know the identity" of the novel material. In Enzo Biochem, 296 F.3d at 1326, this court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003) the court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." These evolving principles were applied in Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004), where the court affirmed that the human antibody there at issue was not adequately described by the structure and function of the mouse antigen; and in University of Rochester v. G.D. Searle & Co., 358 F.3d 916, 925-26 (Fed. Cir. 2004), where the court affirmed that the description of the COX-2 enzyme did not serve to describe unknown compounds capable of selectively inhibiting the enzyme.
>
> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are

known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh.

The Federal Circuit held that the vast disclosure in the art of the nucleotide and amino acid sequences was more than sufficient to provide written description for the claimed invention by both Capon and Eshhar.

In the present case, the state of the art with respect to EGF has been discussed *supra*. Given the extensive number of sequences known in the art, the understanding with respect to the structure and function of EGF and the Federal Circuit decision in *Capon v. Eshhar, Id.*, Applicants do not bear the burden of reproducing the entire body of art with respect to EGF in the specification to illustrate possession of the genus of EGF molecules. Further, given the state of the art with respect to the structure-function relationship of EGF known in the art, the burden does not fall on Applicants to provide each and every species of a claimed genus of molecules.

Applicants submit that, given the state of the art, the specification shows that Applicants were in possession of "EGF" molecules covering the full scope of the currently recited claims at the time the application was filed. Thus, withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is believed to be in order. Such action is respectfully requested.

7. Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hoeprich (Hoeprich, Jr., P.D. et al., The Journal of Biological Chemistry, 254(32): 19086-19091, 1989).

Presently claim 1 recites "[a] A vaccine composition containing human TGFα "hTGFα", wherein said hTGFα comprises the amino acid sequence of SEQ ID NO 2 or its combination with other EGF-R ligands, coupled with any carrier protein by genetic cloning before expression of said proteins or by chemical conjugation after expression of said proteins, wherein said vaccine contains an adjuvant, wherein said vaccine is able to produce a specific immune response against said hTGFα, and wherein said carrier protein is P64k."

Hoeprich does not teach or suggest a vaccine composition as currently claimed wherein said carrier protein is P64k as required by the claims. Thus, withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is believed to be in order. Such action is respectfully requested.

## CONCLUSION

Applicants respectfully request prompt and favorable action with regard to pending claims 1, 2 and 4 through 13. Further, Applicants respectfully request rejoinder and allowance of amended method claims 14-19.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (858) 350-2300.

Respectfully submitted,

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